REVIEW 10.1111/j.1469-0691.2011.03586.x

Filariasis in Africa—treatment challenges and prospects

A. Hoerauf[1], K. Pfarr[1], S. Mand[1], A. Y. Debrah[2,3] and S. Specht[1]

1) *Institute for Medical Microbiology, Immunology and Parasitology, University Hospital Bonn, Sigmund Freud Strasse, Bonn, Germany,* 2) *Faculty of Allied Health Sciences, Kwame Nkrumah University of Science and Technology and* 3) *Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR), Kumasi, Ghana*

Abstract

Lymphatic filariasis (LF) and onchocerciasis are parasitic nematode infections that are responsible for a major disease burden in the African continent. Disease symptoms are induced by the immune reactions of the host, with lymphoedema and hydrocoele in LF, and dermatitis and ocular inflammation in onchocerciasis. *Wuchereria bancrofti* and *Onchocerca volvulus*, the species causing LF and onchocerciasis in Africa, live in mutual symbiosis with *Wolbachia* endobacteria, which cause a major part of the inflammation leading to symptoms and are antibiotic targets for treatment. The standard microfilaricidal drugs ivermectin and albendazole are used in mass drug administration programmes, with the aim of interrupting transmission, with a consequent reduction in the burden of infection and, in some situations, leading to regional elimination of LF and onchocerciasis. Co-endemicity of *Loa loa* with *W. bancrofti* or *O. volvulus* is an impediment to mass drug administration with ivermectin and albendazole, owing to the risk of encephalopathy being encountered upon administration of ivermectin. Research into new treatment options is exploring several improved delivery strategies for the classic drugs or new antibiotic treatment regimens for anti-wolbachial chemotherapy.

Keywords: Albendazole, AWOL, diethylcarbamazine, DOLF, filarial diseases, ivermectin, treatment and research aspects, *Wolbachia*
Article published online: 24 May 2011
Clin Microbiol Infect 2011; **17:** 977–985

Corresponding author: A. Hoerauf, Institute for Medical Microbiology, Immunology and Parasitology, University Hospital Bonn, Sigmund Freud Strasse 25, 53105 Bonn, Germany
E-mail: hoerauf@microbiology-bonn.de

Introduction

The major forms of human filarial nematode infections that may lead to severe pathology are lymphatic filariasis (LF) caused by *Wuchereria bancrofti* and *Brugia* spp., and onchocerciasis caused by *Onchocerca volvulus.* LF can present as recurrent debilitating fevers, lymphangitis, hydrocoele and lymphoedema [1,2]. Onchocerciasis can present as severe dermatitis or visual impairment [3,4]. Severe morbidity from these diseases hinders the development of communities in developing countries [5–7]. Combined, LF and onchocerciasis are responsible for the loss of 6.3 million disability-adjusted life years (disease burden for a population calculated as the years of life lost owing to death or disability as compared with a population living without disease and disability [8]) [9]. In Africa, an estimated 406 million people are at risk for LF and another 102 million are at risk for onchocerciasis [1,2].

Here, we review the major filarial infections of humans in Africa, describing the biology of the parasites and the associated pathologies that develop as a result; current treatments aimed at eliminating the diseases by breaking the transmission cycle of the parasites, including co-endemicity with loiasis, which interferes with the treatment of onchocerciasis; and two consortia funded by the Bill and Melinda Gates Foundation that aim to increase the efficacy of current treatment regimens and to discover new treatments targeting the essential *Wolbachia* endosymbionts of LF and onchocerciasis.

Biology of LF, Onchocerciasis and Loiasis

LF is caused by the most disfiguring parasitic nematodes in humans: *W. bancrofti*, *Brugia malayi* and *Brugia timori*. Whereas brugian filariasis is frequent in Southeast Asia, *W. bancrofti* is the only species causing swelling of the legs and male genita-

lia in Africa. The parasite life cycles include a sexually dimorphic adult stage that occurs in the lymphatic system of the human host. After maturation, the adults produce thousands of first-stage larvae (microfilariae (MF)). *W. bancrofti* MF are present in the peripheral blood during the night. This evolutionary aspect of periodicity is an adaptation to the biting behaviours of mosquitoes of the genera *Aedes*, *Anopheles*, *Culex* and *Mansonia*. The vectors take up MF during blood meals, allowing the filariae to undergo two further moults into the infective L3 stage for transmission to a new, final host [10].

Unlike in LF, in onchocerciasis the white, hair-like adult worms live coiled in subcutaneous or deeper intramuscular tissues surrounded by a fibrous capsule. Within this nodule, the MF are born and migrate through subcutaneous, conjunctival and intraocular tissues. They can live for several months before being taken up by the intermediate host for their moulting into the infective L3 larval stage. Six sibling species of the *Simulium damnosum* sensu lato complex are the vectors of *O. volvulus* in West Africa. Most *Simulium* species lay their eggs attached to rocks and vegetation submerged in highly oxygenated stretches of rivers and streams, where larval and pupal stages develop. The flight range of *Simulium* is up to 12 km, and transmission areas are therefore linked to the breeding sites, giving the common disease name 'river blindness' [10].

Loa loa is confined to Africa in an area spanning from Benin to Gabon (Fig. 1). Prior to ivermectin treatment, it was considered to be only a nuisance infection, because of the lack of debilitating phenotypes [11]. The adult worms migrate freely through the subcutaneous tissues, occasionally crossing superficially through subconjunctival tissues, where they can be easily observed. This manifestation resulted in the colloquial name 'tropical eye worm', but this should not be confused with the disease caused by *O. volvulus*, where MF invade deeper eye tissues. MF of *L. loa* are taken up by the day-biting species of the genus *Chrysops*, commonly known as mango or deer flies [10].

Because all filariae reproduce sexually, and larvae require passage through the intermediate host, or vector, any increase in adult worm burden necessarily implies re-exposure to infective third-stage larvae. Other filarial infections, caused by *Mansonella* spp. and *Dirofilaria* spp., will not be discussed in this review.

Clinical Manifestations

The above-mentioned filarial species differ in the pathologies that they induce, according to the different tissue tropism of their life-cycle stages. Bancroftian filariasis is characterized by lymphoedema (elephantiasis; Fig. 2a) or hydrocoele (swelling of the scrotal area), involving dilatation of the lymphatic vessels and extravasation of fluid from the vessels into surrounding tissues [12]. It is thought that a chronic immune stimulus

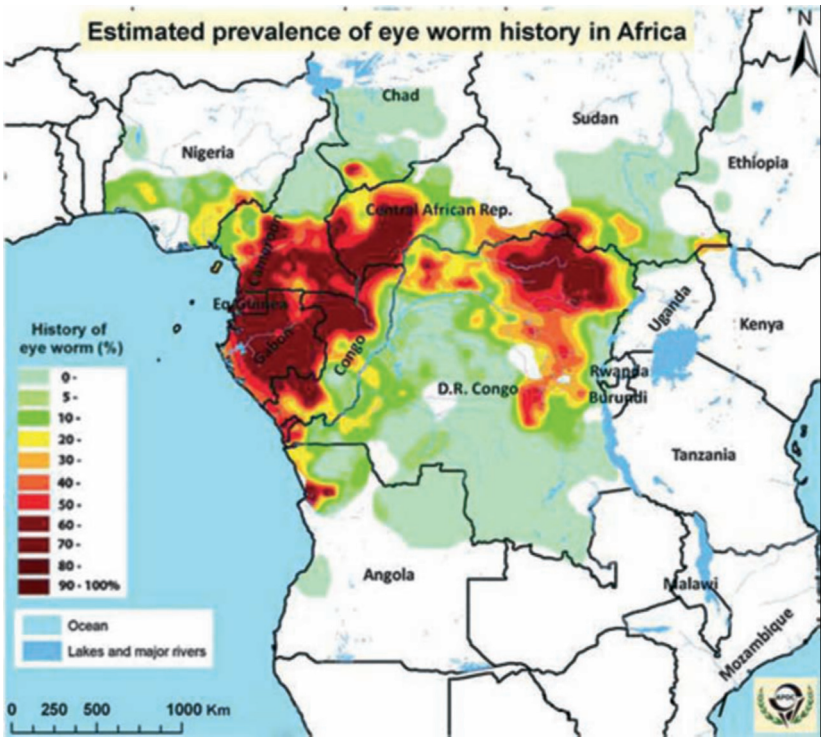

FIG. 1. Map of estimated prevalence of *Loa loa* history in Africa, based on survey data collected in more than 4700 villages in 11 countries.